REMARKS

Reconsideration and allowance are respectfully requested. The Office Action incorrectly states that claim 1 was amended on January 5, 2009. Only claims 4 and 16 were amended.

Claims 1-11 and 15-20 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. For example, the amendment of claim 1 (i.e., describing how pregelatinised starch is produced) is based, inter alia, on the specification at page 2, lines 32-33, and the *European Pharmacopoeia* (2002), which was included in the specification by reference, at page 1438. A corresponding amendment is made to the specification to describe production of pregelatinised starch. Note that the cited page 1438 of *European Pharmacopoeia* (2002) is of record in this application, but another copy is attached for the Examiner's convenience. Claim 20 is based on original claim 1 and the specification at page 2, lines 30-32. Entry of these amendments to the specification and claims will reduce the issues on appeal.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-11 were rejected as allegedly anticipated by MITRA et al. (U.S. Patent 5,955,105) as evidenced by HANDBOOK (*Handbook of Pharmaceutical Excipients, 5th Ed.*, pp. 134, 725 and 731, 2006) and MSDS (*Material Safety Data Sheet*: L-thyroxine, sodium salt). Applicants traverse because their claim 1 is directed to a pharmaceutical formulation comprising:

(a) an effective amount of levothyroxine sodium,

(b) microcrystalline cellulose having a mean particle size of less than 125 μm and present in an amount of 60 to 85% w/w, and

(c) pregelatinised starch present in an amount of 5 to 30% w/w which is produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying.

Alternatively, claim 20 defines 'pregelatinised starch' as containing about 5% free amylase, 15% free amylopectin, and 80% unmodified starch. Neither pharmaceutical formulation is disclosed by MITRA.

MITRA disclosed stabilised pharmaceutical preparations containing levothyroxine sodium. Stabilisation was achieved using a water-soluble glucose polymer (e.g., maltodextrins at column 4, lines 15-16) and a partially soluble or insoluble cellulose polymer (see claim 1). Example 10 of MITRA used microcrystalline cellulose as the partially soluble or insoluble glucose polymer and starch as the water-soluble glucose polymer. Contrary to assertions made in previous Office Actions, MITRA's starch is not synonymous with 'pregelatinised starch' as used in Applicants' claimed invention.

The requirement of the present claims to include pregelatinised starch clearly has different solubility characteristics as compared to MITRA's formultaions. Additionally, pregelatinised starch has a number of other different chemical and physical properties as compared to either specific water-soluble glucose polymers (e.g., starch). In particular, pregelatinised starch has enhanced flow and compression characteristics as compared to unmodified starch: pregelatinised starch granules occur as either irregular chunks or thin plates, whereas unmodified starch occurs as a powder comprising very small spherical or ovoid granules.

Accordingly, since the pharmaceutical formulations of Applicants' claims include pregelatinised starch whereas MITRA's pharmaceutical formulations include a water-soluble glucose polymer (e.g., unmodified starch), novelty is established. Therefore, MITRA does not anticipate the present claims. Applicants submit that this distinguishing feature of their claimed invention (i.e., pregelatinised starch) is sufficient to distinguish over the cited document so any other incorrect allegations about its disclosure are not disputed here, but the opportunity to dispute them in the future is reserved.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. A claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-11 were rejected under Section 103(a) as allegedly unpatentable over MITRA as evidenced by HANDBOOK and MSDS in view of EDQM (*European Pharmacopoeia*, pg. 1438, 2002) and Franz et al. (U.S. Patent Publ. 2003/0032675). Applicants traverse.

The failure of MITRA to disclose the claimed invention as discussed above is not remedied by the attempt to combine that disclosure with EDQM and FRANZ. MITRA disclosed stabilised pharmaceutical preparations containing levothyroxine sodium (column 1, lines 12-14), a water-soluble glucose polymer (e.g., maltodextrin at column 4, lines 15-16), and a partially soluble or insoluble cellulose polymer (see claim 1). In

Example 10 of MITRA, the partially soluble or insoluble cellulose polymer is microcrystalline cellulose and the water-soluble glucose polymer is unmodified starch.

In contrast, Applicants' claims differ from what is disclosed in MITRA (particularly Example 10 therein) in that the present invention employs pregelatinised starch instead of unmodified starch. As noted above, characteristics of pregelatinised starch that distinguish over MITRA's water-soluble glucose polymer are recited in the present claims.

FRANZ disclosed an apparatus and a method for manufacturing thyroid hormone preparations, such as levothyroxine sodium, in tablet form. It did not discuss the nature of the excipients used in the levothyroxine sodium tablets, nor the amounts of excipients, nor how such excipients can affect the stability and disintegration characteristics of the tablets. It merely disclosed a number of commercially available formulations of levothyroxine sodium identified by their tradenames: i.e., Levoxyl, Synthroid, Unithroid, and Soloxine (see page 1, left column, fourth paragraph). Claim 6 of FRANZ recites a formulation of levothyroxine sodium, lactose, microcrystalline cellulose, pregelatinised starch, and magnesium stearate. But no quantities of the various excipients were provided, and there was no suggestion that this combination has any particular advantage over other commercially available formulations of levothyroxine sodium. Moreover, no evidence was presented that it would have been obvious to modify the formulation in Example 10 of MITRA by using the specific excipients of FRANZ's specific formulation in claim 6 with a reasonable expectation of success. Further, since MITRA makes it essential to use a water-soluble glucose polymer, one of ordinary skill in the art would not have had a reason to consider obvious its replacement by pregelatinised starch.

Applicants note that one of ordinary skill in the art would also have had no reason to use MITRA's Example 10 as the starting point for modifying a pharmaceutical formulation because neither stability nor dissolution data were provided as reference points to determine improvement. Even if one of ordinary skill in the art were to combine what is disclosed by claim 6 of FRANZ and Example 10 of MITRA, there is nothing provided in the Office Action to conclude with a reasonable expectation of success that such a combination would result in a formulation having the particularly advantageous stability

and disintegration characteristics as disclosed in Applicants' specification (see data and discussion on pages 7-11 under "Conclusions").

Formulations according to the present invention have the surprising (and totally unexpected) property that those with a higher moisture content (4.1 or 4.7%) display higher stability than those with a lower moisture content (2.4 or 2.7%). These results are shown in Table (C) at page 10 of Applicants' specification; the conclusions are summarized at page 7, lines 39-41, of Applicants' specification.

This characteristic of Applicants' claimed invention is in clear contrast to MITRA's formulations, wherein the latter having a higher moisture content are found to be less stable than those having a lower moisture content. MITRA discloses that for some of the formulations, those with a moisture content of 4.5% are unstable whereas those with a moisture content of 3% are stable (column 4, lines 50-58). MITRA teaches away from the formulations claimed by Applicants because MITRA prefers a moisture content of 0-3% is preferred. Therefore, the problem facing one of ordinary skill in the art is that the formulations disclosed in MITRA must be produced in such a way as to minimize their moisture content in order for them to be stable. This would not have led to Applicants' claimed pharmaceutical formulations.

One of ordinary skill in the art starting from MITRA's formulations and modifying them by replacing MITRA's water-soluble glucose polymer (e.g., unmodified starch in Example 10) with FRANZ's pregelatinised starch would not have predicted that this change would have resulted in the surprising (and totally unexpected) property that the resultant formulations display increasing stability with higher moisture content. As was discussed above, this is a complete reversal of the property of MITRA's formulations which display increasing stability with lower, almost minimal, moisture content. The property of Applicants' claimed pharmaceutical formulations having greater stability at higher moisture content has a number of advantages in terms of being able to control adjustment of the moisture content in order to select specific stability characteristics.

Therefore, for all of the above reasons, it is submitted that the present claims are not obvious over the cited documents. Applicants submit that these features of their claimed invention are sufficient to distinguish over the cited documents so any other

incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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Identification
Dissolve 20 mg in the minimum volume of *chloroform* and evaporate to dryness in a current of nitrogen at room temperature. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of stanozolol *(RS 322)*.

Specific optical rotation In a 1% *w/v* solution in *chloroform*, +34° to +40°, calculated with reference to the dried substance, Appendix V F.

Related substances Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel H* as the coating substance and a mixture of 90 volumes of *chloroform* and 10 volumes of *methanol* as the mobile phase. Apply separately to the plate 5 µl of each of two solutions of the substance being examined in a mixture of 1 volume of *methanol* and 4 volumes of *chloroform* containing (1) 2.0% w/v and (2) 0.010% w/v. After removal of the plate, allow it to dry in air, spray with *ethanolic sulphuric acid (20%)*, heat at 105° for 15 minutes and examine under *ultraviolet light (365 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Loss on drying When dried to constant weight at 100° at a pressure not exceeding 0.7 kPa, loses not more than 1.0% of its weight. Use 1 g.

Assay Dissolve 0.7 g in 50 ml of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end point potentiometrically. Each ml of 0.1M *perchloric acid VS* is equivalent to 32.85 mg of $C_{21}H_{32}N_2O$.

Storage Stanozolol should be kept in a well-closed container and protected from light.

Action and use Anabolic steroid.

Preparation
Stanozolol Tablets

Pregelatinised Starch

Pregelatinised Starch complies with the requirements of the 3rd edition of the European Pharmacopoeia [1267]. These requirements are reproduced after the heading 'Definition' below.

When Pregelatinised Starch is prepared from *Zea mays*, the title Pregelatinised Maize Starch may be used.

Ph Eur

DEFINITION

Pregelatinised starch is starch, apart from wheat starch, that has been mechanically processed in the presence of water, with or without heat to rupture all or part of the starch granules and subsequently dried. It contains no added substances but it may be modified to render it compressible and to improve its flow characteristics.

CHARACTERS

A white or yellowish-white powder, swelling in cold water.

IDENTIFICATION

A. Examined under a microscope using a mixture of equal volumes of *glycerol R* and *water R* it presents irregular, translucent, white or yellowish-white flakes or p... an uneven surface. Under polarised light, (be... crossed nicol prisms), starch granules with a di... cross intersecting at the hilum may be seen.

B. Disperse 0.5 g in 2 ml of *water R* without he... add 0.05 ml of *iodine solution R1*. A reddish-viol... colour is produced.

TESTS

pH *(2.2.3)*. Shake 5.0 g with 25.0 ml of *carbon dio... water R* for 60 s. Allow to stand for 15 min. The p... solution is 4.5 to 7.0.

Iron *(2.4.9)*. Shake 0.75 g with 15 ml of *dilute hy... acid R*. Filter. The filtrate complies with the limit te... iron (20 ppm).

Oxidising substances *(2.5.30)*. It complies with the ... for oxidising substances.

Sulphur dioxide *(2.5.29)*. Not more than 50 ppm.

Foreign matter *(2.8.2)*. Examined under a microsco... using a mixture of equal volumes of *glycerol R* and *wat...* not more than traces of cell walls and of cytoplasmic ... residues are present.

Loss on drying *(2.2.32)*. Not more than 15.0 per cent... determined on 1.000 g by drying in an oven at 130°C ... 90 min.

Sulphated ash *(2.4.14)*. Not more than 0.6 per cent, ... determined on 1.0 g.

Microbial contamination Not more than 10^3 bacteria ... and not more than 10^2 fungi per gram, determined by ... plate-count *(2.6.12)*. It complies with the test for ... *Escherichia coli* *(2.6.13)*.

STORAGE

Store in a well-closed container.

LABELLING

The herbal origin of Starch, pregelatinised is stated.

Stearic Acid

Stearic Acid complies with the requirements of the 3rd editio... the European Pharmacopoeia [1474]. These requirements ... reproduced after the heading 'Definition' below.

Action and use Pharmaceutical aid.

Ph Eur

DEFINITION

Stearic acid is obtained from fats or oils from a vegetable ... or animal source and is a mixture consisting mainly of ... stearic acid ($C_{18}H_{36}O_2$; M_r 284.5) and palmitic acid ($C_{16}H_{32}O_2$; M_r 256.4). It contains different nominal amounts of $C_{18}H_{36}O_2$: stearic acid 50 contains 40.0 per ... cent to 60.0 per cent, stearic acid 70 contains 60.0 per ... cent to 80.0 per cent and stearic acid 95 contains at least ... 90.0 per cent of $C_{18}H_{36}O_2$. The sum of the contents of ... $C_{18}H_{36}O_2$ and $C_{16}H_{32}O_2$ is not less than 90.0 per cent for ... stearic acid 50 and stearic acid 70 and not less than 96.0 per cent for stearic acid 95.

Correspondence between Ph Eur general methods and Appendices of the British Pharmacopoeia is shown on page A8